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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,772	PETIT ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 13, 2004 has been entered.

Status of the Application

2. Claims 3-6 and 8-10 are pending and are rejected herein. This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

Scope of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* infection appears to play a role in the development of the atherosclerosis, using the ketolides of the claimed invention, does not reasonably provide enablement for treating any patient with atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

MPEP 2164.01 states:

> Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation. These factors include, but are not limited to:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

The claims are drawn to a method of treating atherosclerosis in a patient comprising selecting a patient with atherosclerosis and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable salts sufficient to treat atherosclerosis in said patient.

These claims are drawn to patients who have developed atherosclerosis and do not have a *Chlamydia pneumoniae* infection. However, the specification teaches that the ketolides of the invention are only active against *Chlamydia pneumoniae*, and that *Chlamydia pneumoniae* "appears" to play a role in atherosclerosis. Specifically, the specification states,

> The infectious agent *Chlamydia pneumoniae* appears to play a role in the development of atherosclerosis in man. The ketolides are active against *Chlamydia pneumoniae*. As a

> result, the anti-infectious properties against *Chlamydia pneumoniae*...allow them to be used to combat the development of atherosclerosis".

(See page 6, lines 28-35). Accordingly, the specification only teaches the ketolides are active against *Chlamydia pneumoniae* infection.

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

As stated above, the specification on page 6, teaches the following syllogism:

Chlamydia pneumoniae appears to play a role in the development of atherosclerosis in man. Ketolides are active against *Chlamydia pneumoniae*. Therefore, ketolides can be used to treat atherosclerosis.

Accordingly, the specification's assertion of treating atherosclerosis is based solely on the anti-*Chlamydia pneumoniae* activity of the ketolides. Thus, the specification provides guidance as to the treatment of humans having atherosclerosis in which a *Chlamydia pneumoniae* infection appears to play a role in the development of the atherosclerosis. However, the specification does not teach any guidance as to treating any individual having atherosclerosis and not having a *Chlamydia pneumoniae* infection.

In addition, the specification teaches a single example demonstrating an in vitro platelet aggregation test. (See page 9). This Example demonstrates the comparison of a "product P", aspirin and platelet aggregation, from blood taken from rabbits. The specification also states, "P_1, P_2 and P_3 ...also show 'good activity' on this in vitro platelet aggregation test". (See page 9). However, the specification does not provide any correlation between this assay and treating atherosclerosis. Applicants, at best, have taught that P- P_3 shows "good activity" in an in vitro

platelet aggregation test. However, these results do not provide the skilled artisan the requisite guidance for treating any individual with atherosclerosis.

It is noted that the art teaches the use of antiplatelet aggregation tests are unpredictable and take long periods of time to fully develop adequate results. Specifically, Kullo et al. (MAYO Clinic Proceedings (2000) 75(4): 369-80, previously cited) teaches while,

> Spontaneous platelet aggregation was a useful marker for survival and secondary coronary events among a cohort of patients *followed up for 5 years*...diverse measurements of platelet function...*are technically difficult to perform*. Physicians must distinguish between spontaneous platelet aggregation, which is induced by circulating agonists in the blood, and the response of platelets to agonists added externally.

(pg. 372)

Therefore, the state of the art teaches the high quantity of experimentation needed and the unpredictability of carrying out antiplatelet aggregation tests. The specification's teachings do not remedy this high quantity of experimentation or unpredictable level of experimentation.

It is also noted that the state of the prior art has not demonstrated that atherosclerosis is definitively caused by *Chlamydia pneumoniae*.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of

ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In the instant case, neither the art, nor the specification provides the necessary guidance or experimentation to enable one skilled in the art to treat any individual with atherosclerosis. As demonstrated above, the specification provides limited guidance as to the treatment of atherosclerosis. Specifically, the specification only teaches treatment of humans having atherosclerosis in which a *Chlamydia pneumoniae* infection "appeared" to play a role in the development of the atherosclerosis. The specification does not provide any examples of treating any individual (e.g., any mammal) with atherosclerosis (e.g., comprising individuals that do not have a *Chlamydia pneumoniae* infection) with the ketolides of the invention.

In order to perform the experimentation required by the invention, the skilled artisan would have to obtain a cohort of individuals (e.g., any mammal) having atherosclerosis (e.g., comprising individuals that do not have a *Chlamydia pneumoniae* infection) and a control group of individuals not having atherosclerosis, treat the individuals with the ketolides of the invention and measure the effect of the ketolide treatment. Given the lack of guidance in the specification and the art, the results of this experimentation would be unpredictable, as the results would be based on a trial and error process with little to no starting point given by the specification. In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Leadlay et al. (USPN 6,437,151).

The claims are drawn to a method of treating atherosclerosis in a patient comprising selecting a patient with atherosclerosis and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable salts sufficient to treat atherosclerosis in said patient.

However, as discussed in the above 112, 1st paragraph rejection, the claims are only enabled for a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* infection appeared to play a role in the development of the atherosclerosis, using the ketolides of the claimed invention.

Leadlay teaches a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the atherosclerosis, using ketolides

(see col. 4-11 and Examples 16-18, especially col. 11, lines 11-14). With respect to Claim 10, Leadlay teaches the daily dosage is between 0.1-100 mg/kg (col. 12, lines 13-15).

7. Claims 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Masamune et al. (USPN 6,025,350).

The claims are drawn to a method of treating atherosclerosis in a patient comprising selecting a patient with atherosclerosis and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable salts sufficient to treat atherosclerosis in said patient.

However, as discussed in the above 112, 1st paragraph rejection, the claims are only enabled for a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* infection appeared to play a role in the development of the atherosclerosis, using the ketolides of the claimed invention.

Masamune teaches a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the atherosclerosis, using ketolides (see col. 1-15 and 65-72, especially col. 8, lines 41-43). With respect to Claim 10, Leadlay teaches the daily dosage is between 0.2-200 mg/kg (col. 35, lines 20-27).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shor et al. (USPN 5,424,187, previously cited), in view of Agouridas et al. (USPN 5,747,467, previously cited).

The claims are drawn to a method of treating atherosclerosis in a patient comprising selecting a patient with atherosclerosis and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable salts sufficient to treat atherosclerosis in said patient.

However, as discussed in the above 112, 1st paragraph rejection, the claims are only enabled for a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* infection appeared to play a role in the development of the atherosclerosis, using the ketolides of the claimed invention.

Shor teaches methods for treating arterial chlamydial granulomatous disease using anti-*Chlamydia pneumoniae* agents, such as erythromycins (see abstract; col. 2, line 67 to col. 3, line 10; col. 6, lines 49-56; col. 12, lines 40-54, for example). Shor further teaches that

atherosclerotic lesions (i.e., atherosclerosis) result from chlamydial granulomatous disease (see col. 7, lines 22-44 and Examples 2-8). Accordingly, Shor teaches treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the atherosclerosis, using erythromycins.

While Shor teaches the treatment using anti-*Chlamydia pneumoniae* agents, such as erythromycins, Shor does not teach using a ketolide, which is an erythromycin derivative.

However, Agouridas teaches ketolides are anti-*Chlamydia pneumoniae* agents (see col. 5). Specifically, Agouridas teaches a method of combatting Chlamydia infections in warm-blooded animals including humans comprising, administering to warm-blooded animals an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts (col. 5, ln. 33-38). With respect to Claims 3-6 and 9, Agouridas teaches the claimed ketolides (see cols. 1-5 and Example 3). With respect to claim 10, the reference teaches that the usual daily dose is 1.5 to 6 mg/kg, and therefore, provides a range equivalent to the range provided in claim 10 (col. 5, lines 40-42). For example, if the daily dose was at 4mg/kg, and an individual to whom the ketolide was administered weighed 100 kg, then 400 mg would be administered to said individual per day.

Accordingly, in view of the teachings of Agouridas, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shor so as to have used the ketolides of Agouridas. One of ordinary skill in the art would have been motivated to modify the method of Shor, by using a ketolide of Agouridas, in order to have achieved the benefit of providing an effective method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the

atherosclerosis. The ketolides of Agouridas would have provided Shor with the anti-*Chlamydia pneumoniae* agent necessary for inhibiting the granulomatous process, and therefore, providing an effective therapeutic treatment for a patient suffering from atherosclerosis.

11. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shor et al. (USPN 5,424,187, previously cited), in view of Agouridas et al. (USPN 5,635,485).

The claims are drawn to a method of treating atherosclerosis in a patient comprising selecting a patient with atherosclerosis and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable salts sufficient to treat atherosclerosis in said patient.

However, as discussed in the above 112, 1st paragraph rejection, the claims are only enabled for a method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* infection appeared to play a role in the development of the atherosclerosis, using the ketolides of the claimed invention.

Shor teaches methods for treating arterial chlamydial granulomatous disease using anti-*Chlamydia pneumoniae* agents, such as erythromycins (see abstract; col. 2, line 67 to col. 3, line 10; col. 6, lines 49-56; col. 12, lines 40-54, for example). Shor further teaches that atherosclerotic lesions (i.e., atherosclerosis) result from chlamydial granulomatous disease (see col. 7, lines 22-44 and Examples 2-8). Accordingly, Shor teaches treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the atherosclerosis, using erythromycins.

While Shor teaches the treatment using anti-*Chlamydia pneumoniae* agents, such as erythromycins, Shor does not teach using a ketolide, which is an erythromycin derivative.

However, Agouridas teaches ketolides are anti-*Chlamydia pneumoniae* agents (see col. 6). Specifically, Agouridas teaches a method of combatting Chlamydia infections in warm-blooded animals including humans comprising, administering to warm-blooded animals an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts (col. 6, ln. 55-59). With respect to Claims 3-6 and 9, Agouridas teaches the claimed ketolides (see cols. 1-6 and Examples 1-44). With respect to claim 10, the reference teaches that the usual daily dose is 0.6 to 4 mg/kg, and therefore, provides a range equivalent to the range provided in claim 10 (col. 6, lines 62-64). For example, if the daily dose was at 4mg/kg, and an individual to whom the ketolide was administered weighed 100 kg, then 400 mg would be administered to said individual per day.

Accordingly, in view of the teachings of Agouridas, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shor so as to have used the ketolides of Agouridas. One of ordinary skill in the art would have been motivated to modify the method of Shor, by using a ketolide of Agouridas, in order to have achieved the benefit of providing an effective method of treating a human with atherosclerosis, in which *Chlamydia pneumoniae* appeared to play a role in the development of the atherosclerosis. The ketolides of Agouridas would have provided Shor with the anti-*Chlamydia pneumoniae* agent necessary for inhibiting the granulomatous process, and therefore, providing an effective therapeutic treatment for a patient suffering from atherosclerosis.

Conclusion

12. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
March 29, 2004

CARLA J. MYERS
PRIMARY EXAMINER